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Craniosynostosis, Philadelphia Type: A New Autosomal Dominant Syndrome With Sagittal Craniosynostosis and Syndactyly of the Fingers and Toes

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The acrocephalosyndactyly syndromes (ACS) are a group of clinically similar disorders that share the manifestations of craniosynostosis and a variety of hand and foot anomalies. Here we report on a 5-generation kindred segregating sagittal craniosynostosis and syndactyly of the fingers and the toes in an autosomal dominant manner. The anomalies seen in this kindred comprise a syndrome distinct from other craniosynostosis syndromes. For this novel syndrome, we propose the name *craniosynostosis, Philadelphia type*. © 1996 Wiley-Liss, Inc.

KEY WORDS: craniosynostosis, syndactyly, acrocephalosyndactyly

INTRODUCTION

The association of craniosynostosis and hand and foot anomalies is well-known, the classic examples being the acrocephalosyndactyly (ACS) syndromes. These are a group of pathogenetically related syndromes, which include Apert, Saethre-Chotzen, Crouzon, Pfeiffer, and Jackson-Weiss. Some of these syndromes are related at a molecular level as well, with mutations in fibroblast growth factor receptor-2 (*FGFR2*) found to cause Apert [Wilkie et al., 1995], Crouzon [Reardon et al., 1994], and Jackson-Weiss syndrome [Jabs et al., 1994]. Pfeiffer syndrome has been shown to be heterogeneous [Robin et al., 1994], with mutations in *FGFR1* [Muenke et al., 1994] and *FGFR2* [Rutland et al., 1995; Schell et al., 1995]. The gene for Saethre-Chotzen syndrome has been localized to 7p21 [Brueton et al., 1992] but has not as yet been identified. Recently, the phenotypically and molecularly distinct Boston-type [Warman et al., 1993; Jabs et al., 1993] and Adelaide-type [Adès et al., 1994; Hollway et al., 1995] craniosynostosis syndromes have been described, further expanding the diversity of the craniosynostosis syndrome.

Here we report the clinical findings of eight individuals from a 5-generation kindred segregating an apparently novel type of acrocephalosyndactyly. Findings include sagittal craniosynostosis and complete syndactyly of the hands and feet. While it does share the general manifestations of the ACS syndromes, the specific type of craniosynostosis, the lack of midface hypoplasia and other facial anomalies, and the specific findings of the hands and feet distinguish this from other reported craniosynostosis syndromes.

CLINICAL REPORT

The propositus (Fig. 1a–c) was first evaluated at age 11 months. His length was 72 cm (60th centile) and head circumference (OFC) was 46 cm (50th centile). His cranial shape was asymmetric, with a frontal prominence that was greater on the left, and a dolichocephalic head shape. On palpation, there was ridging of the skull in the area of the sagittal and coronal sutures, and a slight downslant of the palpebral fissures. The interpupillary distance was 4.5 cm (50th centile). The maxillary region was normal, as was the palate.

The limbs were notable for syndactyly involving digits 2–5 of the hands, with synonychia (fused nails) of 3–4. The thumbs were normally formed and placed, and of normal width. However, the remaining digits were completely joined, and appeared short. This impression was confirmed by measurements, as the middle finger to total hand ratio (MF/TH) was 2.5 cm/8.0 cm (<3rd centile). The dermatoglyphics (Fig. 2a) were as follows:

	1	2	3	4	5
Right	UL	UL	*	*	CL
Left	RL	CL	*	*	UL

Triradii were normally placed, as were the palmar creases. The dermatoglyphic patterns of digits 3 and 4 were unusual (*) and do not fit into a standard type of pattern.

The feet showed syndactyly of toes 1–5, although the syndactyly was only partial for digits 4–5. The total foot

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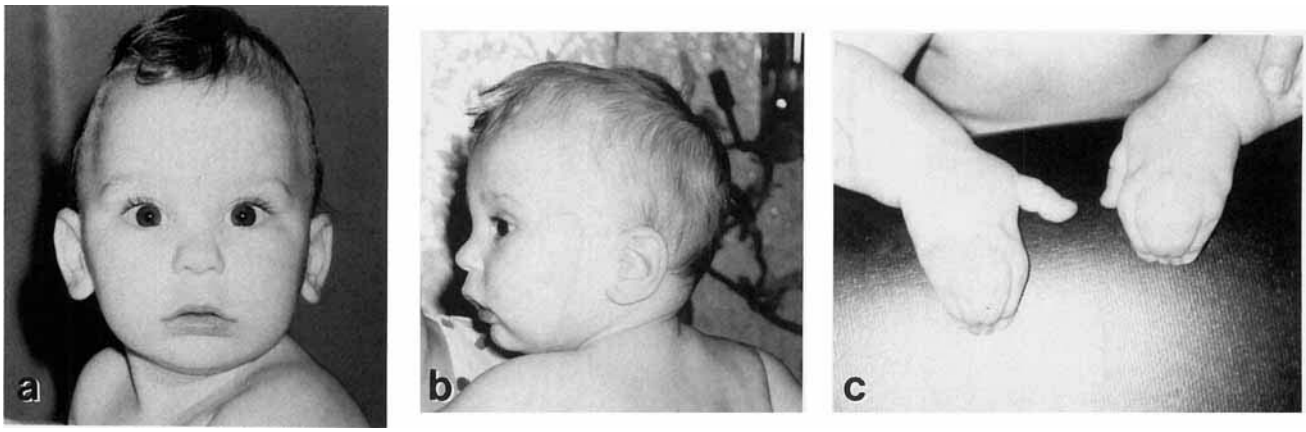

Fig. 1. Propositus (V-4): frontal view (**a**) and profile (**b**), showing the dolichocephalic head shape; preoperative views of the hands (**c**).

length was 12 cm (70th centile). Radiographically, there were no abnormalities of the bones of the feet.

The child had surgical correction of a sagittal synostosis at age 3 months. Clinical and radiographic evaluation (Fig. 3a–c) demonstrated no other abnormal fusion of the cranial sutures. A skeletal survey was normal. The child had no other anomalies, and was developmentally appropriate for age.

The child's father (Fig. 4a–d) had the same hand and foot abnormality. He had soft tissue syndactyly of fingers 2–5, which had been surgically corrected, and complete 1–5 syndactyly of the toes, which was uncorrected. By report, no bony syndactyly was present.

On examination, the father had an OFC of 55 cm (40th centile), with a dolichocephalic head shape. No ridging was apparent to palpation. He had slightly downslanting palpebral fissures, with an interpupillary distance of 6.0 cm (75th centile), and a normally formed maxilla and palate.

His fingers appeared short, and the MF/TH was 7.5 cm/16.5 cm (<3rd centile). His dermatoglyphics (Fig. 2b) were

	1	2	3	4	5
Right	UL	CL	*	*	*
Left	UL	DL	*	*	*

Triradii were normally placed, as were the palmar creases.

The feet were unrepaired, and had 1–5 digit syndactyly. The total foot length was 28 cm (97th centile). There were no other associated anomalies. His intelligence was normal.

The father of the propositus reported that several relatives (Fig. 5) had similar hand and foot anomalies. The clinical findings for the other eight relatives who were personally examined is presented in Table I. Only the propositus had sagittal craniosynostosis that required surgery. However, two others (IV-11 and IV-12) were reported to have required surgery to correct sagittal craniosynostosis. In addition, individuals IV-2, IV-8, IV-9, and V-2 had a dolichocephalic head shape, consistent with an early closure of the sagittal suture.

With one exception all affected individuals manifested the same degree of syndactyly of the hands, digits 2–5, and the feet, digits 1–5. Individual V-5, had syndactyly limited to digits 3–4 bilaterally. In addition, this child is developmentally delayed with spastic cerebral palsy, thought to be related to perinatal complications.

The dermatoglyphics patterns of the affected individuals showed no consistent pattern. However, all af-

TABLE I. Manifestations of Affected Relatives

Individual	III-4	IV-2	IV-8	IV-9	V-2	V-3	V-4	V-5
Age (in years)/sex	55/F	33/M	24/M	25/F	4/M	3/F	1/M	3/M
Sagittal craniosynostosis (7/10)								
with surgical correction (3)[a]	–	–	–	–	–	–	+	na[b]
dolichocephalic head shape (4)	–	+	+	+	+	–	–	na
Downslanting palpebral fissures	–	+	–	+	–	–	+	na
Hands								
Complete soft tissue syndactyly of digits 2–5 (7/8)	+	+	+	+	+	+	+	–
Complete soft tissue syndactyly of digits 3–4 (1/8)	–	–	–	–	–	–	–	+
Middle finger/total hand <3% (7/8)	+	+	+	+	+	+	+	–
Feet								
Complete soft tissue syndactyly of digits 1–5 (8/8)	+	+	+	+	+	+	+	+
Total foot length <3rd centile	–	–	–	–	–	–	–	–

[a] Individuals IV-11 and IV-12 were not examined personally, but were reported to have had surgery for craniosynostosis repair.
[b] Individual had acquired microcephaly, so his craniofacial findings are not included.

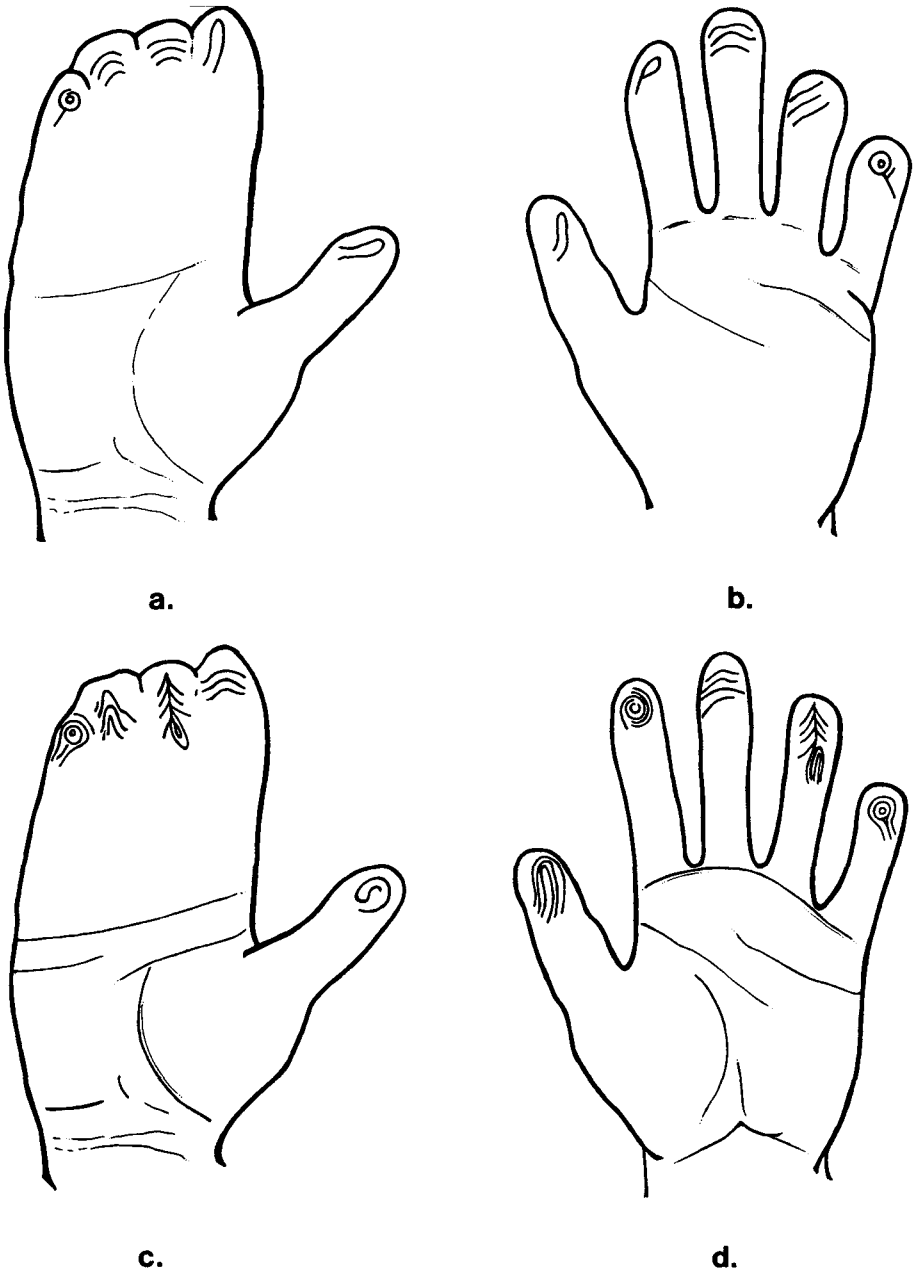

Fig. 2. Representation of the dermatoglyphic patterns observed in individuals V-4 (**a**), IV-8 (**b**), III-4 (**c**), and IV-2 (**d**).

fected individuals did manifest at least one unusual dermatoglyphic pattern on each hand, usually on either digits 3 or 4, or in some cases both. Representative dermatoglyphic patterns for individuals III-4, IV-2, and IV-8 are shown in Figure 2.

Synonychia between fingers 3–4 was present in individuals III-4 (Fig. 6a–d) and V-3 whose hands had not been surgically repaired. Bony syndactyly was present between the terminal phalanges of these two digits in all (4 of 4) preoperative radiographs studied.

All affected individuals had syndactyly of toes 1–5, although some had only partial syndactyly between digits 4–5. There was no synonychia, and no underlying radiographic abnormalities.

Radiographic Studies

Individuals III-4, and V-1 to V-5 have undergone radiographic examinations of the hands and feet. In the children, shortness and apparent sclerosis of terminal digits 2–5 was evident in all but V-1. Bony fusion was present in the distal tip of terminal phalanges 3–4 in V-3 and V-4, but could not be assessed in the remainder of individuals as preoperative films were not available. No other skeletal abnormalities were noted.

Fig. 3. Radiograph of the propositus: (**a**) skull, demonstrating the sagittal synostosis with a dolichocephalic head shape; (**b**) hands, demonstrating hypoplasia and sclerosis of the terminal digits 2–5, and bony syndactyly of the terminal digits 3–4; (**c**) feet, showing no bony abnormalities.

Hand radiographs of individual III-4, the only adult with unrepaired hands who was personally examined, showed a mild progression in the extent of the fusion of the terminal digits 2–5 (Fig. 6e).

Radiographs of the feet in three affected children showed no abnormalities (Fig. 3c). However, in the adult individual (III-4), fusion was evident between terminal digits 2 and 3 of the feet (Fig. 6f), consistent with a mild progression of the bony involvement.

DISCUSSION

Here we present a 5-generation kindred segregating sagittal craniosynostosis and syndactyly of the fingers and toes in an autosomal dominant manner. While this family manifests acrocephalosyndactyly, craniosynostosis and hand, and foot anomalies, the particular findings distinguish it from the other well-described craniosynostosis syndromes (Table II).

The involvement of the sagittal sutures in this family is both distinct and unusual. In other craniosynostosis syndromes, the coronal sutures are involved, usually bilaterally and with full penetrance within a given kindred [Cohen, 1986]. One exception is Berant syndrome [Berant and Berant, 1973], which is the association of sagittal craniosynostosis and radioulnar synostosis. Thus, the occurrence of sagittal craniosynostosis as part of the constellation of abnormalities seen in this family is distinctive.

Sagittal craniosynostosis is the most common type of non-syndromic craniosynostosis, accounting for 56–58%, with a male predominance [Cohen, 1986]. While it is rarely familial, isolated sagittal craniosynostosis has been seen as an autosomal dominant trait [Cohen, 1986]. Furthermore, sagittal craniosynostosis is not commonly associated with other anomalies [Hunter and Rudd, 1976, 1977]. In contrast to familial coronal craniosynostosis, which is fully penetrant with a variable expressivity, familial sagittal craniosynostosis has been seen with reduced penetrance and a male predominance [Cohen, 1986]. Both of these characteristics were evident in this family. Reduced penetrance was observed, as two of eight relatives examined with the hand and foot anomalies (III-4, V-3) had a normal head shape. It is of note that the individuals nonpenetrant for craniosynostosis are all females.

In addition to the difference in the type of craniosynostosis, the normal facial appearance of the affected individuals in this family contrasts with that observed in the other well-described craniosynostosis syndromes. For example, the face of the classic ACS syndromes include hypertelorism, downslant of palpebral fissures, mild to severe midface hypoplasia, ocular proptosis, a high-arched palate, and relative mandibular prognathism. In contrast, only a mild downslant of the palpebral fissures was observed in a few affected individuals in the present family.

The involvement of the hands and feet is consistent within this family. This lack of variability in the degree of syndactyly within a family is not unusual, as such consistency is characteristic of the autosomal dominant forms of the syndactylies [Temtamy and McKusick, 1978]. However, the specific type of syndactyly is distinctive. It is not similar to that reported in any other craniosynostosis syndrome, nor does it fit into one of the five anatomic types described by Temtamy and McKusick [1978]. In the developmental classification proposed by Winter and Tickle [1993], this type of syndactyly would be classified as "normal patterning, abnormal separation with normal number of digits, total hand involvement." The example given for this type of syndactyly is Apert syndrome. While this condition shares the 2–5 syndactyly that can be seen in Apert type, the absence of significant bony syndactyly and other bony abnormalities distinguishes the hands and

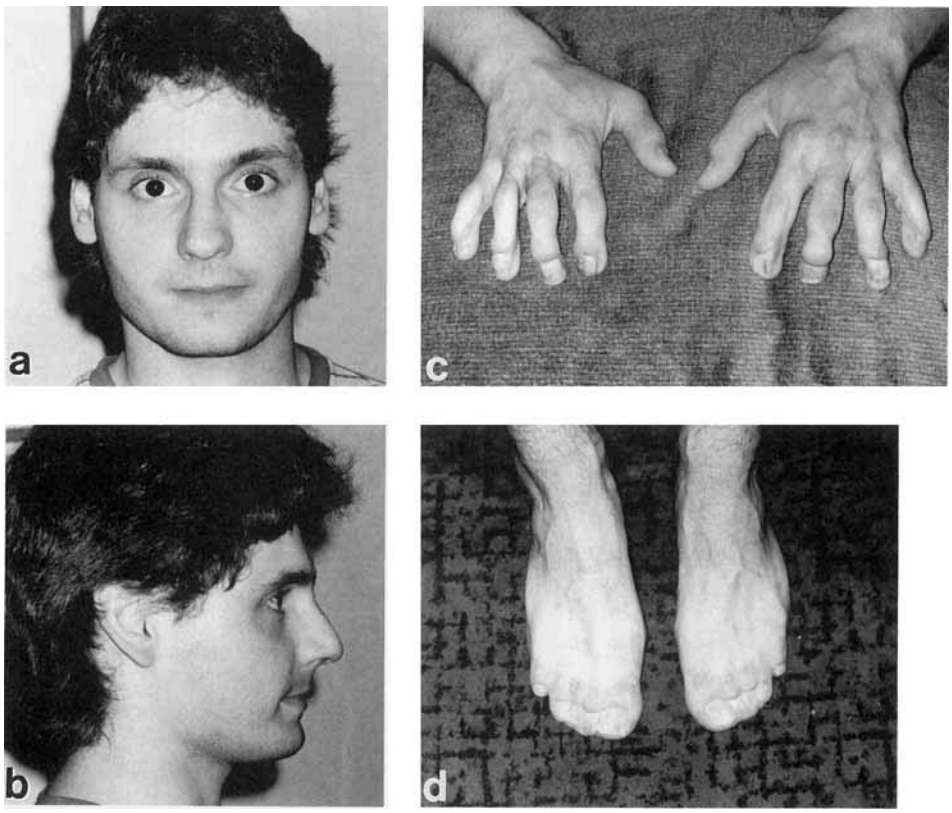

Fig. 4. The propositus' father (IV-8): frontal view (**a**) and profile (**b**), demonstrating the mild dolichocephalic head shape; repaired fingers (**c**), and unrepaired feet (**d**).

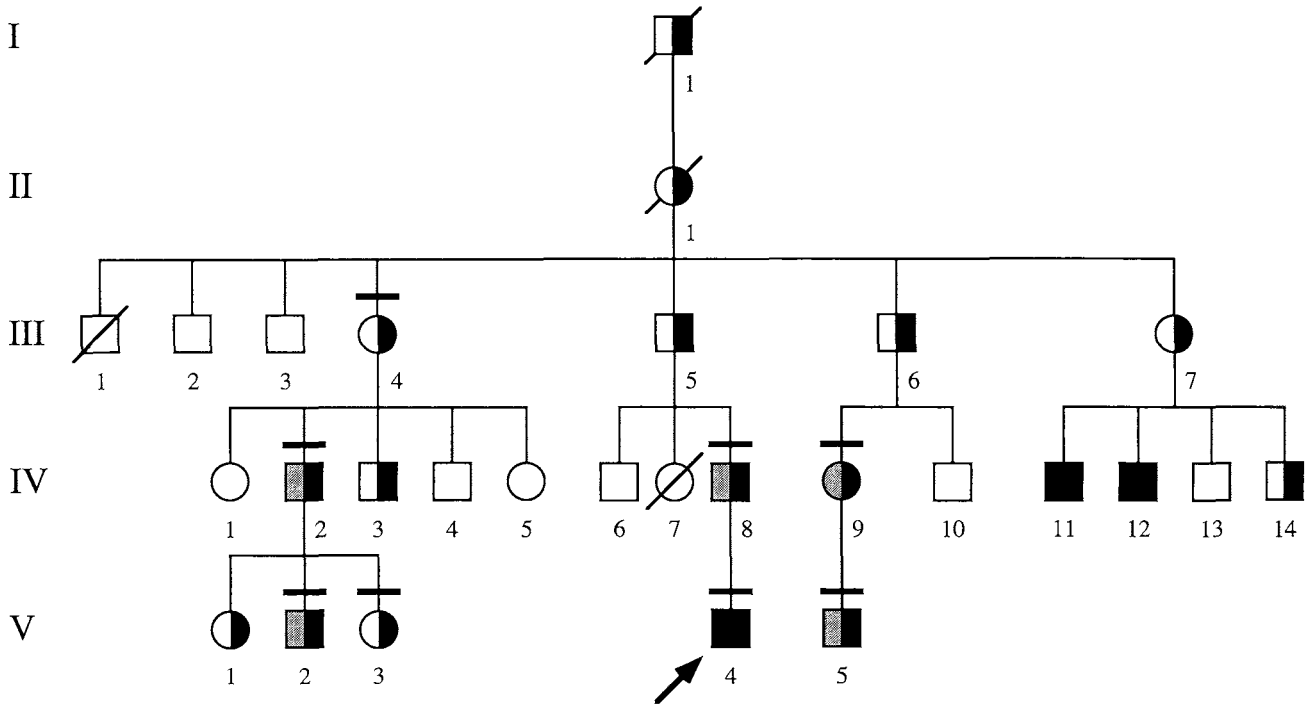

Fig. 5. Pedigree. The arrow indicates the propositus and the bar above the symbols individuals examined. ■, Syndactyly of fingers and toes with sagittal craniosynostosis; ◨, syndactyly of fingers and toes; and ▩, syndactyly of fingers and toes with dolichocephaly.

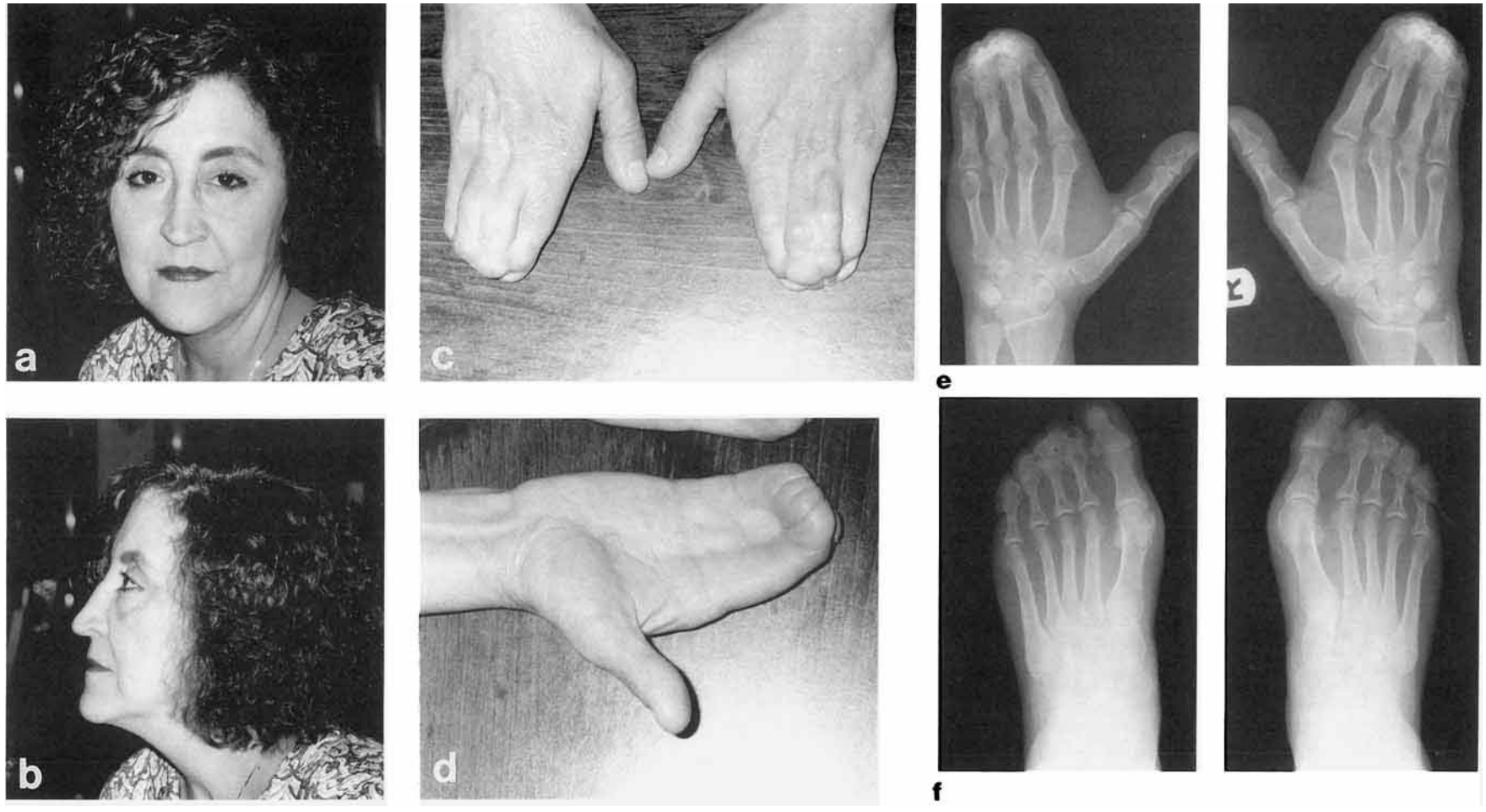

Fig. 6. Individual III-4: frontal view (**a**), profile (**b**), dorsal (**c**), and ventral view (**d**) of unrepaired hands; radiographs of hands (**e**), showing bony fusion of terminal digits 2–5, and the feet (**f**), showing fusion of terminal digits 2 and 3.

TABLE II. Comparison of Craniosynostosis, Philadelphia Type With Other Autosomal Dominant Craniosynostosis Syndromes

Syndrome	Gene	Craniosynostosis/face	Hand/foot	Additional anomalies
Philadelphia	??	Sagittal/dolichocephalic head shape in most; male > female normal facies	Complete soft tissue syndactyly of digits 2–5/1–5; X-ray: hypoplasia and sclerosis of terminal phalanges	None
Apert	*FGFR2*	Coronal; severe midfacial hypoplasia, HT,* proptosis	Complete soft tissue and bony syndactyly of digits 2–4 minimally	MR* common
Saethre-Chotzen	??[a]	Coronal; HT, ptosis facial asymmetry	Variable brachysyndactyly, broad and laterally deviated thumbs and great toes	MR, short stature
Pfeiffer	*FGFR1* *FGFR2*	Coronal; mild to severe midfacial hypoplasia and proptosis	Brachydactyly, with broad and medically deviated thumbs and great toes	Occasional MR, elbow ankylosis, hearing loss
Crouzon	*FGFR2*	Coronal; severe midfacial hypoplasia and ptosis, HT	None	Strabismus, hearing loss
Jackson-Weiss	*FGFR2*	Coronal; mild to severe midfacial hypoplasia and proptosis, HT	Brachydactyly,with broad and medially deviated great toes; normal thumbs	Occasional MR
Boston	*MSX2*	Variable suture involvement; four clinical subtypes: a) fronto orbital recession, b) frontal bossing, c) turribrachycephaly, d) cloverleaf skull	None	Headache, poor vision, seizures
Adelaide	??[b]	Coronal synostosis, facial asymmetry, ptosis, prognathia	Brachydactyly of fingers and toes	Hearing loss, short stature

* HT, hypertelorism; MR, mental retardation.
[a] Saethre-Chotzen has been linked to 7p21 [Brueton et al., 1989].
[b] Adelaide has been linked to 4pter [Hollway et al., 1995].

feet in this family from those seen in Apert syndrome [Cohen and Kreiborg, 1995]. In the Apert syndrome, the bony fusion may not be apparent neonatally, as only cartilaginous structures are present. Later, as these structures ossify, the bony fusion becomes apparent. Within this family the degree of bony fusion was somewhat more extensive in the unrepaired adult (III-4) possibly due a to mild progression of the bony involvement.

This apparently novel syndrome, for which we propose the name *craniosynostosis, Philadelphia type,* continues to expand the diversity of this group of disorders. Recent work has greatly expanded our understanding of the molecular basis of the craniosynostosis syndromes. It will be interesting to learn if this disorder is genetically related to other ACS syndromes, or is molecularly distinct, thus pointing to another gene important in craniofacial and limb development.

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